临床研究

腺苷三磷酸合酶抑制因子1在女性生殖系统正常及病变组织中的表达

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摘要:目的 了解腺苷三磷酸(ATP)合酶抑制因子1 (IF1)在女性生殖系统正常及病变组织中的表达,为进一步探索其生理功能及治疗女性生殖系统疾病新方法提供依据。**方法** 以近2年内在我院手术切除的女性生殖系统正常及病变组织为研究对象,组织取自25~69岁患者,包括正常子宫内膜38例、异位症在位及异位内膜各33例、子宫内膜腺癌30例、正常子宫肌壁24例、子宫肌瘤30例、正常宫颈18例、宫颈鳞癌30例、正常输卵管11例、输卵管腺癌19例、正常卵巢15例、卵巢腺癌21例、绒毛及蜕膜各30例。采用免疫组化检测IF1在各样本中的表达,采用Western blot和RT- PCR法,检测IF1及其mRNA在正常子宫内膜、异位症在位及异位内膜中的表达。**结果** IF1在子宫内膜腺癌($P<0.01$)、宫颈鳞癌($P<0.01$)、输卵管腺癌($P<0.01$)、卵巢腺癌($P<0.01$)组织表达均较对应正常组织显著增强,但在子宫肌瘤与正常子宫肌壁、绒毛与蜕膜间未见显著差异;在正常子宫内膜组织中,IF1在分泌期表达较增殖期显著减少($P<0.01$)。此外,IF1在异位症异位内膜表达较异位症在位内膜($P<0.05$)及正常内膜($P<0.01$)均显著增高,但异位症在位内膜与正常内膜间无显著差异。RT-PCR结果显示,IF1 mRNA表达在正常内膜、异位症在位内膜、异位症异位内膜表达均无显著差异。**结论** IF1在女性生殖系统正常及非恶性病变组织中均有不同程度阳性表达,但在恶性肿瘤组织中表达异常增高,该结果提示IF1可作为女性生殖系统恶性肿瘤标记物,有望成为女性生殖系统恶性肿瘤新的治疗靶点。

关键词:合酶抑制因子1;女性生殖系统;恶性肿瘤;子宫内膜异位症

Expression of ATPase inhibitory factor 1 in normal and pathological tissues of female reproductive system

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Abstract: Objective To determine ATPase inhibitory factor 1 (IF1) expression in normal and pathological tissue of female reproductive system to better understand the physiological role of IF1 in malignancies of the female reproductive system. **Methods** Surgical specimens of normal tissues and primary malignant tumors were obtained during the past 2 years, including 38 normal endometrium tissues, 33 endometriosis tissues, 30 endometrial adenocarcinoma tissues, 24 uterine myoideum tissues, 30 uterine fibroid tissues, 18 normal cervical tissues, 30 cervical squamous carcinoma tissues, 11 fallopian tube tissues, 19 fallopian tube adenocarcinoma tissues, 15 ovarian tissues, 21 ovarian endometrial adenocarinoma tissues, 30 decidua tissues, and 30 villus tissues. The expressions of IF1 protein and mRNA were assessed by immunohistochemistry, Western blotting and RT-PCR. **Results** The expressions of IF1 were significantly increased in endometrial adenocarcinoma ($P<0.01$), cervical squamous carcinoma ($P<0.01$), fallopian tube adenocarcinoma ($P<0.01$) and ovarian endometrial adenocarinoma ($P<0.01$) as compared with those in normal tissues. In normal endometrium, IF1 expression was significantly reduced in the secretory phase as compared with the proliferation phase ($P<0.01$). In patients with endometriosis, IF1 protein expression increased obviously in endometriotic tissues as compared with eutopic and normal endometrial, but the expression IF1 mRNA was similar among the 3 tissues. **Conclusion** IF1 expression, increases abnormally in malignant tumors of the female reproductive system and may serve as a marker for malignancies of the female reproductive system as well as a promising pharmacological target for cancer treatment.

Key words: ATPase inhibitory factor 1; female reproductive system; malignant tumour; endometriosis

众所周知,真核生物主要通过糖酵解和氧化磷酸化两种途径完成能量代谢,获得ATP。研究发现,在肿瘤组织能量代谢过程中,糖酵解与氧化磷酸化间存在相互制约、此消彼长的关联[1-2];因此,酵解增强且氧化磷酸化减弱被认为是肿瘤增殖旺盛的标志[3];反之,当氧化磷酸化增强且糖酵解减弱,则往往意味着肿瘤增殖受抑、进展延缓[4-5]。ATP合酶抑制因子1(IF1)是一种内源性小分子蛋白,可通过抑制ATP合酶(ATPase)功能,从而抑

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制氧化磷酸化并促进糖酵解[6-7]。研究证实,IF1活化与pH值密切相关。大量由糖酵解所产生的乳酸,可导致肿瘤组织内环境pH值降低,促使IF1活化形成二聚,并结合两个单位F1-ATPase,从而导致ATPase功能受抑[8],并最终促进肿瘤细胞增殖、侵袭和存活[9-10]。因此有学者认为,IF1是一个潜在的致瘤因子,可作为肿瘤早期诊断及复发、转移的预测指标[11-13]。

目前,关于IF1在女性生殖系统正常及病变组织中表达的系统研究尚未见报道。为此,本研究将通过检测IF1在女性生殖系统正常及病变组织中的表达,初步了解IF1与低氧能量代谢及细胞增殖、细胞恶性转化的关联,为进一步探索其生理功能及治疗女性生殖系统疾病新方法提供依据。

1 材料和方法

1.1 样本来源及处理

全部试验设计及操作流程均已经过解放军总医院伦理委员会批准,并获得患者书面知情同意。样本选自2013~2015年我院患者手术切除的组织(表1),患者均月经周期规律,且术前3个月均无激素治疗史。肿瘤组织样本均取自初次手术且未经放化疗的患者(25~69岁);其余组织取自手术患者(25~49岁),其中正常肌壁和子宫肌瘤取自同一患者因子宫肌瘤行子宫全切术的组织,正常子宫内膜组织取自因子宫肌瘤手术的组织,子宫异位症在位内膜及异位病灶取自同一患者子宫内膜异位症手术切除的组织,蜕膜及绒毛组织来自早孕8~10周行人工流产的组织,正常输卵管来自宫外孕行手术切除的组织,正常卵巢来自子宫内膜卵巢异位手术切除的组织。样本以4%中性多聚甲醛液固定,常规石蜡制片;其中部分子宫内膜及异位病灶样本以4 ℃生理盐水洗去血液后,迅速置于液氮中低温冻存待用。

1.2 免疫组化法检测IF1表达

石蜡切片脱蜡至水,以EDTA抗原修复缓冲液(pH9.0)微波修复,3% H_2O_2阻断内源性过氧化物酶10 min,PBS浸洗,3%BSA室温封闭10 min,以IF1一抗(1∶50, ab197806, Abcam, USA)4 ℃孵育过夜,PBS浸洗,加二抗(K500711, Dako, Denmark)室温孵育1 h,PBS浸洗,DAB(K500711, DAKO, Denmark)显色,苏木素复染,常规脱水、透明、封片。随后每张切片200×光镜下观察,随机取3个视野拍照,图像采用CMIAS软件(CMIAS, Beijing University of Aeronautics and Astronautics, China)进行分析,得到每个视野中对应抗原表达的面密度,求出每张切片的均值。

1.3 Western blotting法检测IF1含量

低温冻存的组织,常规提取总蛋白,采用BCA法进行蛋白定量,以4×上样缓冲液稀释后,95 ℃热变性15 min后作为样本。样本上样量50 μg,12% SDS-PAGE电

表1 样本类型及例数
Tab.1 Characteristics and number of the samples

Sample	Abbreviation	Number of samples
Endometrium (proliferative)	EN-P	32
Endometrium (secretory)	EN-S	6
Eutopic endometrium from EMs	EU	33
Ectopic endometrium from EMs	EC	33
Adenocarcinoma of endometrium	ET	30
Uterine myoideum	UN	24
Uterine fibroids	UF	30
Normal cervix	CN	18
Squamous carcinoma of cervix	CT	30
Fallopian tubes	FN	11
Adenocarcinoma of fallopian tube	FT	19
Ovary	ON	15
Ovarian endometrial adenocarinoma	OT	21
Decidua	D	30
Villus	V	30

泳,转PVDF膜,5%脱脂奶粉室温封闭1 h,TBS-T浸洗,以IF1(1∶50, ab197806, Abcam, USA)、β-actin(1∶100, ab16039, Abcam, USA)一抗4 ℃孵育过夜,TBS-T浸洗,以HRP标记的二抗(BS13278, Bioworld, USA)室温孵育1 h,TBS-T浸洗,ECL发光液显色(BLH01S020, Bioworld, USA),随后以凝胶扫描成像及图像分析系统(SCA/fluorCho, Alpha Inotech, USA)观察拍照,并对结果进行灰度值分析,随后求出IF1/β-actin的比值作为IF1的相对表达量。

1.4 RT-PCR法检测IF1 mRNA表达

低温冻存的组织,经液氮充分碾磨后,加入Trizol reagent (15596-026, Invitrogen, USA)常规提取RNA。引物信息为:IF1-forward 5'-GGGCCTTCGGAAAGAGAG-3'; IF1-reverse 5'-TTCAAAGCTGCCAGTTGTTC-3'; β-actin-forward 5'-GGAGATTACTGCCCTGGCTCCTA-3'; β-actin-reverse 5'-GACTCATCGTACTCCTGCTTGCTG-3'。随后依次配制以下液体,A液:样本RNA 9 μL,加入Random primer 1 μL,70 ℃金属浴5 min,立即0 ℃冷却5 min;B液:采用GoScript Reverse Transcription system(Promega, USA),参照说明书,配制10 μL Reverse Transcription mix;混合A、B液,25 ℃退火5 min,42 ℃延伸1 min,70 ℃灭活逆转录酶5 min,完成cDNA合成。随后采用SYBR Green PCR Master

Mix (Applied Biosystems, USA) 配制反应体系,设定仪器 7500Real Time PCR System (Applied Biosystems, USA) 40个PCR循环(95 ℃ 15 s, 60 ℃ 1 min)进行扩增,并读取各样本目的基因和内参基因的Ct值,随后计算出目的基因/内参基因的相对表达量,每个样本进行3个复孔实验,取均值作为该样本目的基因表达量。

1.5 统计学分析

数据以均数±标准差表示,采用SPSS 17.0软件进行单因素方差分析,以$P<0.05$认为差异具有统计学意义。

2 结果

2.1 IF1在女性生殖系统恶性肿瘤中呈强阳性表达

免疫组化结果显示(图1A),IF1在女性生殖系统正常组织中均有不同程度表达,其中增殖期子宫内膜表达最强(++),宫颈上皮、输卵管上皮及卵巢次之(+),子宫肌壁表达最弱(+/-);在绒毛、蜕膜及女性生殖系统恶性肿瘤组织中,IF1则均呈强阳性表达(+++)。图像分析统计结果显示(图1B),与对应来源的正常组织比较,子宫内膜腺癌($P<0.01$)、宫颈鳞癌($P<0.01$)、输卵管壶腹部腺癌($P<0.01$)、卵巢内膜样腺癌($P<0.01$)IF1表达均显著增加,但绒毛与蜕膜、正常子宫肌壁与子宫肌瘤之间,IF1表达无显著差异。

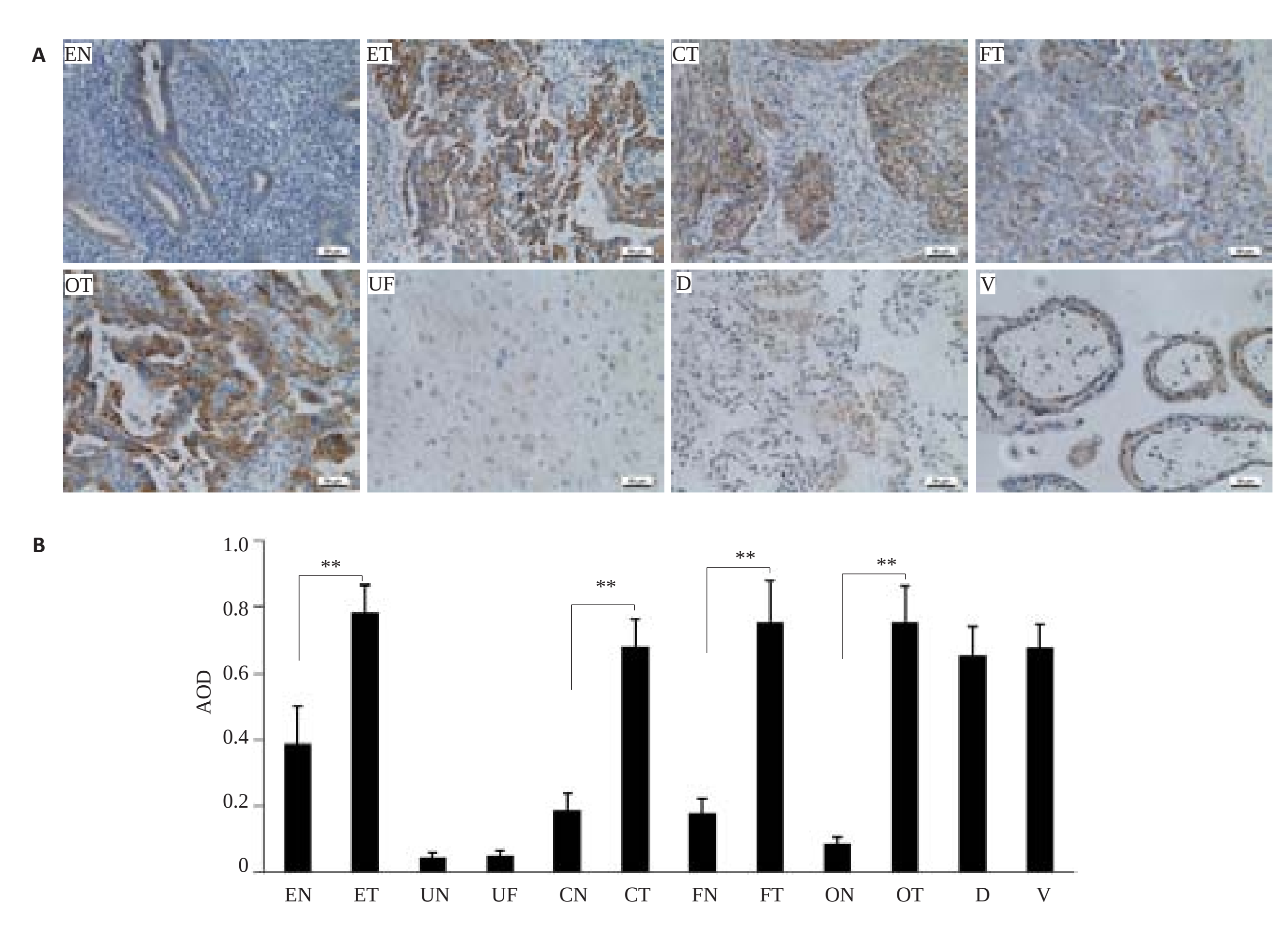


图1 IF1在女性生殖系统及其原发肿瘤组织中的表达

Fig.1 Expression of IF1 in nomal andmalignant tissues of the female reproductive system. *A*: Immunohistochemical results (Original magnification: ×200); *B*: Image analysis results. *$P<0.05$, **$P<0.01$ *vs* normal tissue. EN: Normal endometrium; ET: Adenocarcinoma of endometrium; UN: Normal uterine myoideum; UF: Uterine fibroids; CN: Normal cervix; CT: Squamous carcinoma of cervix; FN: Normal fallopian tubes; FT: Adenocarcinoma of fallopian tube; ON: Normal ovary; OT: Ovarian endometrial adenocarinoma; D: Decidua; V: Villus).

2.2 IF1在增殖期子宫内膜表达高于分泌期

免疫组化结果显示(图2A),IF1在正常增殖期子宫内膜呈阳性表达(++),但在分泌期基本不表达或弱表达(+/-);图像分析统计结果显示(图2B),IF1在增殖期子宫内膜表达显著高于分泌期($P<0.01$)。

2.3 IF1及其mRNA在正常子宫内膜、EMs在位内膜及异位病灶中的表达

免疫组化及Western blot结果显示(图3A,B),IF1在EMs异位病灶表达最强(+++),而在正常子宫内膜及EMs患者原位内膜表达较弱。图像分析统计结果显示

(图3A,B),EMs异位病灶IF1表达较正常子宫内膜(*P*<0.01)及EMs患者在位内膜(IHC-P, *P*<0.01; WB, *P*<0.05)均显著增强。RT-PCR检测统计分析结果显示(图3C),IF1 mRNA在正常子宫内膜、EMs在位内膜及异位病灶中表达未见显著差异(*P*>0.05)。

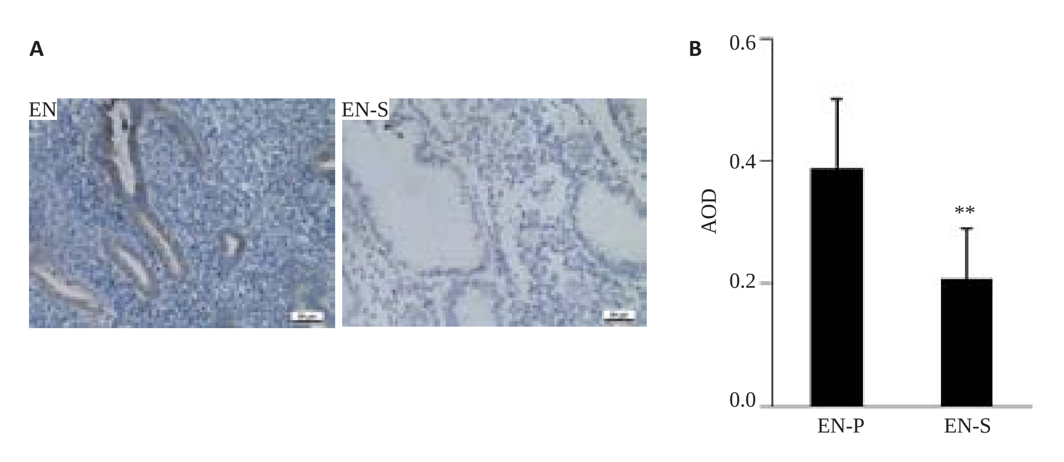


图2 IF1在增殖期及分泌期子宫内膜中的表达

Fig.2 Expression of IF1 in endometrium in the proliferation and secretory phase. *A*: Immunohistochemical results (×200); *B*: Image analysis results. **P*<0.05, ***P*<0.01 *vs* EN. (EN-P: Proliferative endometrium; EN-S: Secretory endometrium).

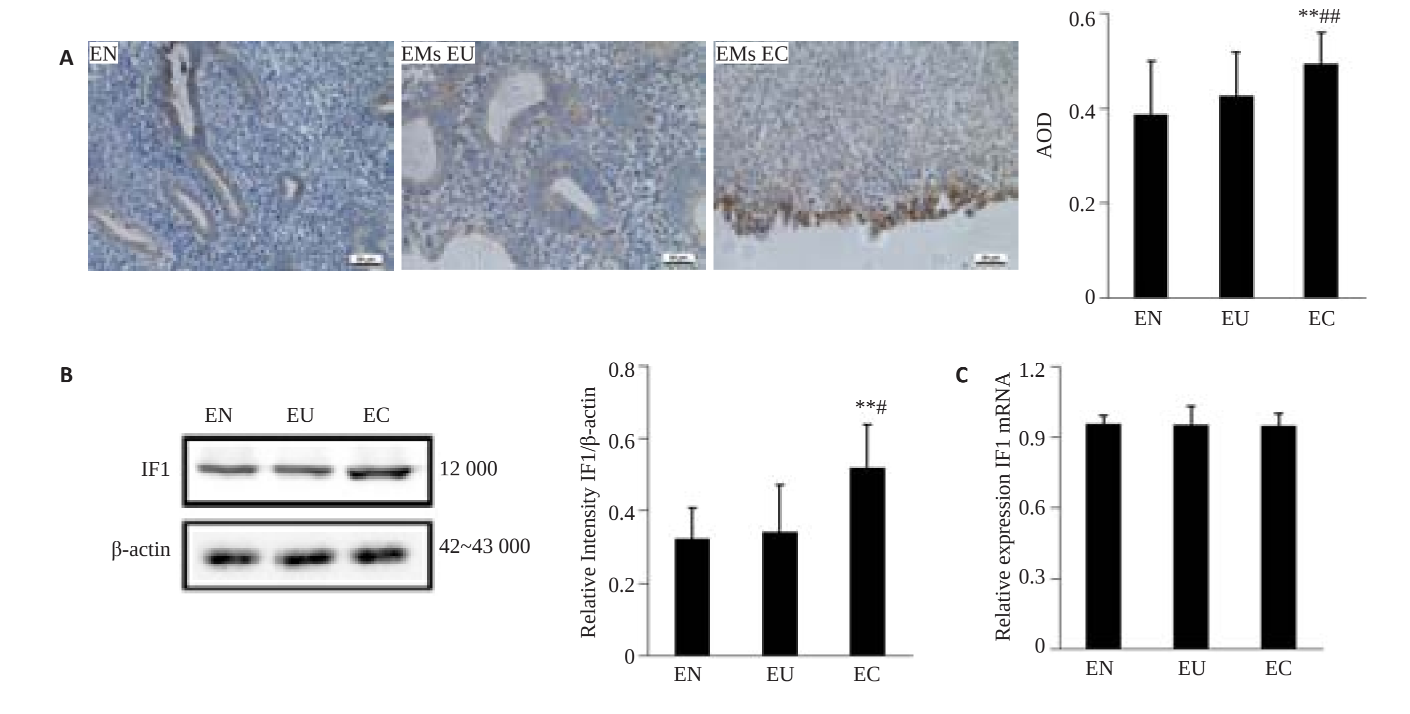


图3 IF1及其mRNA在正常子宫内膜、内异症在位内膜及异位病灶的表达

Fig.2 Expression of IF1 in normal and EMs endometrium. *A*: Immunohistochemical results (× 200); *B*: Western blotting results; *C*: RT-PCR results. **P*<0.05, ***P*<0.01 *vs* EN. #*P*<0.05, ##*P*<0.01 *vs* EU (EN: Normal endometrium; EU: Eutopic endometrium from EMs; EC: Ectopic endometrium from EMs).

3 讨论

以往的研究普遍认为,在肿瘤组织中,由于线粒体发生不可逆损伤,氧化磷酸化途径被高度抑制,肿瘤主要通过糖酵解途径获取能量,这一独特的能量代谢方式又被称为“Warberg效应”[14]。在糖酵解过程中,产生的ATP虽然较少但速度快,并可产生乳酸等适于肿瘤增殖的产物,为肿瘤生长微环境创造良好条件,因此糖酵解较氧化磷酸化更加适合肿瘤快速生长的需要[15-16, 33]。目前,多种以抑制糖酵解为作用机理的药物(例如:2-脱氧葡萄糖、氯尼达明等)已被应用于临床,用于控制肿瘤的

生长，但其往往对生长迅速的肿瘤有效，而对生长缓慢的肿瘤效果欠佳[17-18]。

在氧化磷酸化过程中，ATPase是其催化作用的核心酶。在正常生理条件下，ATPase可将ADP磷酸化生成高能化合物ATP，从而为细胞提供能量；在缺氧等应激情况下，则可逆向催化ATP水解[19]。研究发现，ATPase表达在多种肿瘤组织中普遍下降[20]，且更低表达的ATPase也被发现与肿瘤耐药性增强和预后不佳存在关联[21-24]。因此有研究认为通过对ATPase表达水平及活性的调控，有可能影响肿瘤的生长和生存[9, 25]。

1963年，Pullman和Monroy首次发现了一种内源性ATPase功能抑制蛋白，并将其命名为ATP合酶抑制因子1[26]。IF1是由10^6~10^9个氨基酸组成的小分子蛋白(10 000)，其基因编码在不同的种属中显示出高度保守性，这也提示了其在生物功能中具有重要地位[27]。研究发现，IF1在肝、肺等多种恶性肿瘤组织中异常增高[6, 13, 28]。本研究结果则显示，IF1在子宫内膜腺癌、宫颈鳞癌、输卵管腺癌，卵巢内膜样腺癌等女性生殖系统恶性肿瘤组织中，表达较其来源的正常组织均异常增高。该结果进一步证实，IF1在恶性肿瘤能量代谢过程中发挥重要作用。

EMs虽然属于良性疾病，但与恶性肿瘤具有相似的生物学习性，具有浸润、复发的特点并有可能发生恶变。有研究指出线粒体功能紊乱是EMs发生的高危因素[29]。本研究发现，与正常内膜及EMs在位内膜比较，EMs异位内膜IF1表达均显著增加。该结果提示，EMs异位内膜的生长及代谢方式与肿瘤细胞类似，有通过糖酵解途径提供能量。但IF1 mRNA表达在正常内膜、EMs在位及异位内膜间，未见明显差异，该结果提示IF1基因存在转录后调控。

有研究认为，从氧化磷酸化转向糖酵解代谢，同时伴随IF1表达增加，是细胞增殖旺盛的表现[30]。本研究发现，正常子宫内膜也有IF1的高表达，并且增生期子宫内膜表达高于分泌期，而在正常子宫及宫颈肌壁均呈极低或低表达。此外，尽管子宫肌瘤组织氧分压(0~5 mmHg)明显低于正常子宫肌壁组织(PO_2, 5~20 mmHg)[31]；且有研究发现由氯化钴诱导的低氧损伤，能够增加体外培养的大鼠肝细胞IF1的表达[32]；但本研究发现IF1在子宫肌瘤及正常子宫肌壁均呈低表达且无显著差异。与此同时，绒毛和蜕膜组织均增殖旺盛，且具有丰富的血供，不存在缺氧状态，在本研究中均发现呈现IF1高表达。以上结果提示，在体内环境中，IF1表达应该与组织是否低氧状态无关，而与其增殖和代谢活性相关。即增殖缓慢、代谢需求较低的组织中IF1呈低表达；增殖旺盛、代谢需求相对高的组织IF1呈高表达。

目前，关于IF1在女性生殖系统的表达，及其与女性生殖系统疾病关联的研究均未见报道。本研究发现，IF1在女性生殖系统正常组织中呈不同程度阳性表达，其表达与组织增殖和代谢活性正相关；IF1在女性生殖系统恶性肿瘤中表达异常增高，并存在转录后调控；IF1有可能通过抑制ATPase功能，参与肿瘤能量代谢的调控，从而影响肿瘤细胞的生存和生长。综上所述，我们认为对女性生殖系统恶性肿瘤，IF1可作为其诊断指标之一，并有可能成为新的治疗靶点。

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